Poster Session II

ALLOGENEIC TRANSPLANTS

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ROLE OF LYMPHOCYTE RECOVERY AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PREDICTING RELAPSE IN PEDIATRIC ACUTE LEUKIMIAS

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for many children with relapsed or high risk acute leukemias both myelogenous (AML) and lymphoblastic (ALL). There are no reliable markers to predict relapse which remain main cause of treatment failure post transplantation with very poor outcome. We hypothesize that early lymphocyte recovery measured by the absolute lymphocyte count (ALC) after HSCT correlate with relapse and survival. Therefore, we evaluated the effect of ALC and risk of relapse by studying ALC on day 21(ALC-21) and day 30(ALC-30) post HSCT in both ALL and AML children. We reviewed 207 consecutive patients with acute leukemias who received allogeneic HSCT between 1994 and 2005 in the Hospital for Sick Children, Toronto, Canada. One-thirty-six transplantations were performed for ALL and 75 transplantations were performed for 71 children with AML. All patients at time of HSCT were in complete morphological remission (CR) except for one AML patient. Remission status were as follows; CR1, n=84; CR2, n=103; CR3, n=23 and one patient with AML had 10% blast just prior to HSCT. Conditioning regimens included; cylcophosphamide/TBI in 110 patients, VP16 and TBI in 59 patients, busulphan and cyclophosphamide in 28 patients and 14 children received other conditioning regimens. Donor stem cells source were; matched sibling donor (MSD) in 98 patients, a mismatched related donor (MMRD) in 21 patients, and 88 children received matched unrelated donor (MUD) and 4 children received cord progenitor stem cells. For ALL, patients with ALC $<0.3\times10^9$/L at day 21 (n=104) had more than 5 times risk of relapse compared to those with ALC count $>0.3 \times 10^9$/L (n=32) (Hazard ratio 1/0.19; P=0.0004). Patients with ALC $<0.3\times10$/L (n=48) at day 30 were more than twice likely to relapse compared to those with ALC $>0.3\times10^9$/L (n=88) (Hazard ratio 1/0.46; P=0.01). Whereas in AML; ALC $<0.3\times10^9$/L or $>0.3\times10^9$/L on day 21 and 30 were not predictive of relapse with a Hazard ratio at day 21; 0.88; P= 0.8), Hazard ratio at day 30; 0.5; P= 0.2. **Conclusion:** Slow lymphocyte recovery after HSCT appears to be associated with a significantly high risk of relapse in ALL but not in AML as analyzed on day 21 and day 30 post HSCT. This group of patients in ALL may benefit from post transplant immune manipulation to prevent relapse. However, in AML early lymphocyte recovery is not predictive of relapse.

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A SUBMYELOABLATIVE REGIMEN OF CAMPATH-1H AND FLUDARABINE FOR PATIENTS WITH GRAFT FAILURE FOLLOWING ALLOGENEIC TRANSPLANTATION FROM MHC IDENTICAL OR NEAR IDENTICAL DONORS

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Primary or secondary graft failure or the persistence or reappearance of mixed chimerism (MC) are potentially serious causes of morbidity and mortality following hematopoietic stem cell transplantation (HSCT). In a phase I/II pilot study we combined Fludarabine with the lympho-depleting humanized anti-CD52 antibody Campath-1H as a non-myeloablative therapy designed to overcome donor-anti-recipient T cell responses and to permit complete and successful donor engraftment following re-infusion of donor stem cells. This study evaluated the safety, feasibility, and rate of donor engraftment for *twenty-two* patients at our institution from September 2000 to June 2006 (median age 3.5 years; range 7 months to 69 years; 14 males) with engraftment failure or mixed chimerism (range 8-61% donor cell chimerism). All patients had previously received one or more transplants for lympho-hematologic malignancies (n=14), immunodeficiency syndromes (n=5) or metabolic diseases (n=3). Twelve patients were enrolled for graft failure (55%) and ten for mixed chimerism (45%). Seven patients were transplanted in relapse (3 with graft failure and 4 with mixed chimerism). The conditioning regimen consisted of Fludarabine and Campath-1H (30mg/m^2/day and 10mg/day, respectively) given on days –5 to –3. Twelve patients received transplants from a single antigen mismatched family donor (55%), nine from a matched unrelated (41%) and one from an HLA-identical sibling. Donors were the same used for the primary transplant. *Twenty-one* evaluable patients (>95%) achieved sustained neutrophil engraftment, and complete donor chimerism by day 28. Regimen-related toxicities were tolerable. Nine patients (41%) never experienced neutropenia. The median time to neutrophil engraftment for those who experienced neutropenia was 10 days (range 2 to 20). The overall survival for non-malignant transplant recipients was 100 % and 43 % for patients with malignant disease, at a median follow-up of 32 months (range, 4 to 73 months). Of the 8 patients who died, 5 succumbed to relapse, while 1 died from infection, 1 from pulmonary and 1 from cardiac toxicity. Only one patient had mild (grade I) acute graft-versus-host disease (aGVHD). We conclude that this reduced-intensity regimen enabled satisfactory engraftment and achievement of rapid complete donor chimerism with minimal toxicities. It was associated with a low incidence of aGHVD. The disease status was the main determinant of treatment failure in this study.

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THE CONDITIONING REGIMEN INTENSITY OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (ALLO-HCT) IN CHRONIC MYELOID LEUKEMIA (CML): THE HISTORICAL CASE MATCHED COMPARISON OF ABLATIVE VERSUS REDUCED INTENSITY REGIMEN

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Allo-HCT is the only curative treatment approach yet. The use of reduced intensive conditioning (RIC) regimen, which has the main advantage of decrease in regimen related toxicity in comparison with myeloablative (MA) regimens, is rising both in our country and throughout the world. In this study we aimed to retrospectively investigate the efficacy of RIC on early and late allogeneic transplant outcome in CML patients.Twenty-five patients conditioned with RIC regimen were matched to 48 patients, who received a myeloablative regimen. The main criteria for case matching among our CML allo transplant cohort were the Gratwohl scoring system (Gratwohl A. Lancet. 1998 352(9134):1087-92). The donors were HLA identical siblings and the graft sources were peripheral hematopoietic cell (n=67) or bone marrow (n=6). Pretransplantation disease status was CP1 (n=17), CP2 (n=2), and advanced phase (AP; accelerated phase plus blastic crisis) (n=6) in RIC group, and CP1 (n=37), CP2 (n=2) and AP (n=18) in MA group. All but one patient in MA group received BU&CY, while FLU-based regimes were used in RIC group. Median age was 39 years (range, 24-57) and M/F was 11/14 in the RIC group, and median age was 38.5 years (19-53 ys) and M/F was 30/18 in MA group. The transplant-related data are shown in Table. The frequency grade and period of mucositis were lower in RIC. As expected days on total parenteral nutrition and febrile neutopenia episodes were seen infrequently in RIC compared to MA. How-

ever, early transplant-related mortality (TRM) was similar in both groups. Besides both the frequency of acute and chronic GvHD were not affected by the intensity of conditioning regimen. In median 24.2 months (0.2-36 ms) of follow-up period, 3-year-probability of DFS and OS in RIC compared to MA were 34.7 % vs 46.9 % (log-analysis, p=0.31) and 61.2 % vs 47.2 % (p=0.37), respectively. **Conclusion:** We observed less regimen related toxicity in RIC group as expected. Although the incidence of disease relapse was more frequent in RIC group than MA group, both DFS and OS were found in similar rates in both regimen. In CML patients RIC regimen could be preferable instead of a MA regimen, in high risk transplant candidates. We have still no evidence for RIC about durable control of CML. After the completion of an ongoing prospective and randomized phase III study in CML comparing the RIC with MA in our center; we will extensively evaluate the impact of RIC at allogeneic transplantation.

Transplantation data

Variables	RIC group (n=25)	p	MA group (n=48)
Median CD34 (10e6/ BW kg) (range)	4.63 (2.49-13.16)	0.283	4.85 (0.36-18.90)
Median MNC (10e8/ BW kg) (range)	4.31 (0.98-19.15)	0.953	4.79 (0.55-19.15)
Median CD3 (10e8/ BW kg) (range)	21.70 (1.00-100.26)	0.071	25.10 (1.0-294.54)
Median Gratwohl Score (range)	2 (1-4)	0.795	2 (1-4)
Engraftment kinetics			
Neutrophil> 0.5×109/L, median days (range)	15 (0-20)	0.699	14 (10-32)
Platelet> 20×109/L, median days (range)	10 (0-15)	<0.0001*	13.5 (8-32)
Mucositis (Present/ Absent)	11/14	<0.0001*	45/3
Median grade of mucositis (range)	0 (0-3)	<0.0001	2 (0-4)
Median days of mucositis (range)	0 (0-14)	<0.0001*	7 (0-20)
Febrile episode (Present/Absent)	11/14	<0.0001*	45/3
Median incidence of febrile episode, n	0 (0-2)	<0.0001*	1 (0-3)
Median days of febrile episode (range)	0 (0-8)	0.008*	2 (0-15)
TPN use	22%	<0.0001*	77%
Acute GvHD	34.8%	0.785	29.8%
Chronic GvHD	76.2%	0.504	72.5%
Early transplant-related mortality	12.0%	0.522	20.8%
Relapse	52%	0.001*	26%
3-year- probability of DFS	34.67% ± 10.62%	0.314	46.85% ± 7.89%
3-year- probability of OS	61.24% ± 10.24%	0.367	47,19% ± 7.85%

*p<0.05

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C-REACTIVE PROTEIN (CRP) MAY PREDICT TRANSPLANT-RELATED MORTALITY AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (HCT)

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Current prognostic factors for transplant related mortality (TRM) are disease status, the presence of comorbid conditions, and performance status. Each of these measures has problems of sensitivity and discriminative capacity. CRP, a marker of systemic inflammation, has shown considerable value in non-HCT setting to predict vascular events and overall survival(OS). We hypothesized that elevated CRP would predict for worse HCT outcome. Using a highly sensitive CRP assay, pre-HCT CRP levels were analyzed in 41 consecutive patients with MDS or AML who underwent HCT after a preparative regimen of fludarabine (125 mg/m2 IV total), melphalan (140 mg/m2 IV total) and alemtuzumab (100 mg IV total). The median age was 52 years and 11/41 had active had active disease at HCT. The median CRP level was 20.6 mg/L and the mean was 38.5 mg/L (range 0.3 to 180). Six month TRM was 23% with a median follow-up for survivors of 15 months. There was a significant association between higher pre-HCT CRP levels and TRM (P= 0.03). CRP levels above the median had a hazard ratio of 3.2 (P = 0.07). CRP also showed an association with overall survival (OS) (P= 0.07) of borderline statistical significance. CRP remained predictive of TRM after adjusting for disease status (P = 0.06), charlson comorbidity index (P = 0.03), kaplan-feinstein comorbidity index (P = 0.01), ECOG performance status (P=0.07) and age over 50 (P=0.04). We conclude that in HCT recipients, the independent prognostic value of CRP for TRM suggests the potential to enhance estimates of HCT outcome in addition to standard prognostic factors. Prospective studies in larger patient cohorts should be pursued to confirm the independent value of CRP and other pro-inflammatory cytokines on HCT outcome.

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THIOTEPA BASED CONDITIONING REGIMEN IN 374 PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTS FROM RELATED OR UNRELATED DONORS

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Background: The Perugia group introduced thiotepa (THIO) in allogeneic stem cell transplants (HSCT): we have developed THIO based conditioning regimens in combination with cyclophopshamide (CY), Fludarabine (FLU), melphalan (MEL) or TBI 200 mainly for patients above the age 45.

Aim of the study: assess the outcome of patients undergoing an allogeneic HSCT with a THIO based conditioning regimen.

Patients. 374 patients were allografted with a THIO based regimen, between 1994 and 2005, from HLA identical siblings (SIB) (n=221) or family partially mismatched (n=67) or unrelated (n=86) donors. Median patient age was 48 years (range16-.67). The stem cell source was unmanipulated in all cases , either bone marrow (n=276) or peripheral blood (n=98). The conditioniong regimens were classified as reduced intensity (n=177) (THIO-CY or THIO-FLU) or intensified (n=197) (THIO+CY supplemented with MEL or TBI). The disease was in 1stCR (n=221) or more advanced phase (n=153). Patients had chronic myeloproliferative disorders (n=123), acute leukemia (n=120), myelodisplasia (n=46), other (n=85, including lymphoma and myeloma). All, patients received cyclosporin methotrexate GvHD prophylaxis; anti-thymocyte globulin was added for alternative donor transplants. The median follow up for surviving patients is 5 years (range 1-12 years)

Results: The overall actuarial *10 year survival is 40%*, (60% vs 30% in CR1 or >CR1 disease). The cumulative incidence (CI) of *transplant related mortality (TRM)* at 10 years is *29%* (18% vs 36% for CR1 or >CR1 disease); *TRM* for CR1 patients grafted from identical siblings (n=94) is 12%. Acute GvHD grade III-IV was seen in 6% of sibling HSCT and 12% of alternative donor grafts. The CI of *relapse related death (RRD)* at 10 years *was 27%* (18% vs 32% in CR1 or >CR1). There was no effect of patient age, nor of stem cell source on survival. In *multivariate analysis on survival*, significant predictors were disease phase (RR 2.4 of death for patients beyond CR1) and intensity of the conditioning (RR 1.66 for intensified regimens); these two variables also predicted TRM; disease phase predicted RRD.

Conclusions: This study shows that THIO based conditioning